self-reactive T cells. A protein called AIRE (autoimmune regulator) stimulates expression of some "peripheral tissue-restricted" self antigens in the thymus and is thus critical for deletion of immature T cells specific for these antigens. Mutations in the *AIRE* gene are the cause of an autoimmune polyendocrinopathy (Chapter 24). In the CD4+ T-cell lineage, some of the cells that see self antigens in the thymus do not die but develop into regulatory T cells (described later).

- When developing B cells strongly recognize self antigens in the bone marrow, many of the cells reactivate the machinery of antigen receptor gene rearrangement and begin to express new antigen receptors, not specific for self antigens. This process is called *receptor editing*; it is estimated that a quarter to half of all B cells in the body may have undergone receptor editing during their maturation. If receptor editing does not occur, the self-reactive cells undergo apoptosis, thus purging potentially dangerous lymphocytes from the mature pool.

Central tolerance, however, is imperfect. Not all self antigens may be present in the thymus, and hence T cells bearing receptors for such autoantigens escape into the periphery. There is similar "slippage" in the B-cell system. Self-reactive lymphocytes that escape negative selection can inflict tissue injury unless they are deleted or muzzled in the peripheral tissues.

Peripheral Tolerance

Several mechanisms silence potentially autoreactive T and B cells in peripheral tissues; these are best defined for T cells. These mechanisms include the following:

- **Anergy. Lymphocytes that recognize self antigens may be rendered functionally unresponsive, a phenomenon called *anergy*.** We discussed earlier that activation of antigen-specific T cells requires two signals: recognition of peptide antigen in association with self MHC molecules on the surface of APCs and a set of costimulatory signals ("second signals") from APCs. These second signals are provided by certain T cell-associated molecules, such as CD28, that bind to their ligands (the costimulators B7-1 and B7-2) on APCs. If the antigen is presented to T cells without adequate levels of costimulators, the cells become anergic. Because costimulatory molecules are not expressed or are weakly expressed on resting dendritic cells in normal tissues, the encounter between autoreactive T cells and their specific self antigens displayed by these dendritic cells may lead to anergy. Several mechanisms of T-cell anergy have been demonstrated in various experimental systems. One of these, which has clinical implications, is that T cells that recognize self antigens receive an inhibitory signal from receptors that are structurally homologous to CD28 but serve the opposite functions. Two of these inhibitory receptors are CTLA-4, which (like CD28) binds to B7 molecules, and PD-1, which binds to two ligands that are expressed on a wide variety of cells. Because CTLA-4 has higher affinity for B7 molecules than does CD28, CTLA-4 may be preferentially engaged when the levels of B7 are low, as when APCs are presenting self antigens. Conversely, microbial products elicit innate immune reactions, during which B7 levels on APCs increase and the low-affinity receptor CD28 is engaged more. Thus, the affinities of the activating and inhibitory receptors and the level of expression of B7 may determine the outcome of T cell antigen recognition. The importance of these inhibitory mechanisms has been established by the finding that mice in which the gene encoding CTLA-4 or PD-1 is knocked out develop autoimmune diseases. Furthermore, polymorphisms in the *CTLA4* gene are associated with some autoimmune endocrine diseases in humans. Interestingly, some tumors and viruses may use the same pathways of immune regulation to evade immune attack. This realization has led to the development of antibodies that block CTLA-4 and PD-1 for tumor immunotherapy—by removing the brakes on the immune response, these antibodies promote responses against tumors.

  Anergy also affects mature B cells in peripheral tissues. It is believed that if B cells encounter self antigen in peripheral tissues, especially in the absence of specific helper T cells, the B cells become unable to respond to subsequent antigenic stimulation and may be excluded from lymphoid follicles, resulting in their death. B lymphocytes also express inhibitory receptors that may play a role in limiting their activation and preventing responses to self antigens.

- **Suppression by regulatory T cells. A population of T cells called *regulatory T cells* functions to prevent immune reactions against self antigens.** Regulatory T cells develop mainly in the thymus, as a result of recognition of self antigens (Fig. 6-21), but they may also be induced in peripheral lymphoid tissues. The best-defined regulatory T cells are CD4+ cells that express high levels of CD25, the α chain of the IL-2 receptor, and a transcription factor of the forkhead family, called FOXP3. Both IL-2 and FOXP3 are required for the development and maintenance of functional CD4+ regulatory T cells. Mutations in *FOXP3* result in severe autoimmunity in humans and mice; in humans these mutations are the cause of a systemic autoimmune disease called *IPEX* (an acronym for *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked). In mice knockout of the gene encoding IL-2 or the IL-2 receptor α or β chain also results in severe multi-organ autoimmunity, because IL-2 is essential for the maintenance of regulatory T cells. Recent genome-wide association studies have revealed that polymorphisms in the *CD25* gene are associated with multiple sclerosis and other autoimmune diseases, raising the possibility of a regulatory T-cell defect contributing to these diseases. The mechanisms by which regulatory T cells suppress immune responses are not fully defined, but their inhibitory activity may be mediated in part by the secretion of immunosuppressive cytokines such as IL-10 and TGF-β, which inhibit lymphocyte activation and effector functions. Regulatory T cells also express CTLA-4, which may bind to B7 molecules on APCs and reduce their ability to activate T cells via CD28.

  Regulatory T cells may play a role in the acceptance of the fetus. Placental mammals face a unique challenge because the developing fetus expresses paternal antigens that are foreign to the mother yet have to be tolerated. There is emerging evidence that regulatory T cells